UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF

PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: October 10, 2001

MEMORANDUM

SUBJECT: **DIURON**: Cancer Classification and Mechanism of Action

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THROUGH: Pauline Wagner, Branch Chief
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DP Barcode:	D278246	**Submission:**	S604292
Chemical:	Diuron	**Case:**	818790
PC Code:	035505	**CAS No.:**	330-54-1

Action: Review and respond to Registrant's submission entitled "Cancer Classification and Mechanism of Action" (MRID 45494501) and mutagenicity studies (MRIDs 45494502-05).

Response: The Reregistration Branch 2 (RRB2) reviewed the submitted data and presented it to the HED Mechanism of Toxicity Assessment Review Committee (MTARC). A pre-screening subgroup of the MTARC evaluated the proposed mechanism of action with the data submitted by the Registrant and concluded that the submitted information is insufficient to support a mode of action on bladder carcinogenicity for diuron. After consulting with the Chair of the Cancer Assessment Review Committee (CARC), **the RRB2 determined that there is insufficient information to support a**

reclassification of cancer category for diuron at this time.

I. Background

Diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea] is a substituted urea herbicide for the control of a wide variety of annual and perennial broadleaves and grassy weeds on both crop and noncrop sites. In 1996, the HED Carcinogenicity Peer Review Committee (CPRC) has classified diuron as a "known/likely" human carcinogen by all routes, based on urinary bladder carcinoma in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse. The CPRC also recommended a low dose linear extrapolation model with Q_1^* of $1.91x10^{-2}$ $(mg/kg/day)^{-1}$ be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the rat.

The Registrant argues that this assessment needs reconsideration for the following reasons: (1) There is no history of human carcinogenesis as the result of diuron exposure. (2) There is a plausible mode of action that discounts the relevance of the rat bladder carcinomas to humans. (3) The mouse historical data was not considered in its entirety and should be considered 'spontaneous'. (4) The structure activity relationships actually decrease the weight-of-the-evidence of diuron carcinogenicity rather than increase the weight, and (5) New guidelines are in place that separate the 'known' from 'likely' category (extracted from pages 7-8 of Registrant's submission, MRID 45494501). The responses of the RRB2 are as follows.

II. The Responses of RRB2

1. There is no history of human carcinogenesis as the result of diuron exposure.

RRB2 Response: The Registrant did not submit any data or information to support its claim; in addition, it cannot be used to rule out any remote possibility of human carcinogenesis as the result of diuron exposure.

2. There is a plausible mode of action that discounts the relevance of the rat bladder carcinomas to humans.

RRB2 Response: The document entitled "Diuron: Cancer Classification and mechanism of Action" (MRID 44302002, resubmitted as MRID 45494501) has been submitted to the HED MTARC for evaluation. The MTARC concluded that the submitted information is **insufficient** to support a mode of action on bladder carcinogenicity for diuron based on the following reasons (extracted from the HED MTARC Report):

(1) The Registrant claimed that a mechanism or mode of action document has been submitted to the

Agency without being reviewed by the CPRC. The pre-screening committee reviewed the document and found that the document is only a report of an analysis using two models (quantal polynomial multistage and Weibull models) to evaluate carcinogenic risk to human of dietary exposure to diuron. This study was not designed to nor was it intended to address a mode of action on bladder carcinogenicity of diuron.

(2) A study entitled "Study for toxicity to Wistar rats with special attention to urothelial alterations, unpublished data" by Schmidt and Karbe (1987) indicated that male Wistar rats were fed diuron in their diet at a concentration of 2500 ppm for 2, 4, 12, or 26 weeks. Recovery groups were similarly treated for 4 or 26 weeks and then observed for 4-8 weeks. Histopathological examination of urinary bladders revealed a treatment-related increased incidence of hyperplasia of the epithelium and an increase in the degree of hyperplasia from a treatment duration of four weeks onwards. Examination of animals in the recovery groups revealed a clear trend toward reversibility of the induced alterations after cessation of treatment. The pre-screening committee concluded that this study suggested a reversibility of possible precancerosis but did not present or propose a mode of action on bladder carcinogenicity for diuron.

(3) The Registrant submitted published literature in an attempt to address the role of diet and pH of the rat urine for supporting the mode of action on bladder carcinogenicity of diuron. The pre-screening committee reviewed these literature reports and determined that these reports were either non-diuron specific or irrelevant to diuron. The Registrant did not provide direct evidence to support a mode of action on dietary influence and high pH value as the mechanism on bladder carcinogenicity for diuron.

(4) The Registrant cited a rat metabolism study on diuron (HED Doc. No. 012408) and stated that there are no common mechanisms among diuron, linuron, and propanil with regard to cancer endpoints. No further information was presented. The pre-screening committee determined that the Registrant did not demonstrate a relevance of the metabolism of diuron to mode of action on bladder carcinogenicity.

(5) The CPRC report (1997) has indicated that diuron was only weakly positive (considered being equivocal) in an *in vitro* cytogenetic study. The Registrant submitted several reports on mouse bone marrow micronucleus study to show that diuron is non-genotoxic. The pre-screening committee referred its decision to latest HIARC Report on mutagenicity (HED Doc. No. 014657, dated August 28, 2001). The HIARC report stated that "diuron was not mutagenic in bacteria or in cultured mammalian cells and no indication of DNA damage in primary rat hepatocytes was observed. There was weak evidence of an *in vivo* clastogenic response in Sprague Dawley rats in one study and statistically significant increases in cells with structural aberrations in a second study conducted with the same rat strain. The data from the latter study, however, were shown to fall within the historical control range." The pre-screening committee concurred with the Registrant that there is little or no concern on mutagenic activity of diuron.

3. The mouse historical data was not considered in its entirety and should be considered 'spontaneous'.

RRB2 Response: The mouse historical data has been reviewed and included in the updated DER (MRIDs 42159501 and 43349301). **It was concluded that a positive oncogenic response was seen in high-dose female mice compared to the control group.** The following conclusions are extracted from the discussion section of the DER.

The study authors presented data from historic controls performed from 1981 to 1988 using mice of the same strain from the same source that showed mammary gland adenocarcinoma incidences that ranged from 0% to 13% with the average frequency being 3.2%. This same source showed ovarian luteoma frequencies ranging from 0% to 7% [Bomhard, E. (1992) Historical control data showing the frequency of tumors in NMRI-mice taken from 18 long-term studies over 21 months, Bayer Report No. 21534]. An additional reference provided historic control data collected from studies done from 1974 through 1981 [Bomhard, E. and Mohr, U. (1989) Spontaneous tumors in NMRI mice from carcinogenicity studies. Exp. Pathol. 36: 129-145]. In the latter reference, the mammary adenocarcinoma average incidence was 3.9% with a range of 0% to 10.8% and the ovarian granulosa cell tumor average frequency was 19.1% with a range of 5.0% to 35.5%. Ovarian luteomas develop from granulosa cells, but were not specifically identified in the reference. Compared to the historic data, the mammary adenocarcinoma incidences seen in the control group in the current study agree well, but the incidences in the high-dose group are at, or slightly above, the upper limit of that seen in control animals. The ovarian luteoma instances seen in the current study are slightly high in the control group and well above the normal range at 2500 ppm compared to the historic control animals; however, the luteoma incidences are not outside the upper range for all granulosa cells derived tumors according to the historic data. The statistical significance of the increased incidences in this study depends on a test for trend; the differences are not statistically significant according to the Fisher's exact test performed by the reviewer. The study authors concluded that the increased incidences of mammary and ovarian neoplasms in high-dose female mice compared to the control group were not treatment-related. This conclusion is questionable because the incidences of spontaneous tumors in normal control populations of this strain of mice vary considerably, and the best control is usually thought to be the one that was performed during the current study. **Under the conditions of this study, a positive oncogenic response was seen in high-dose female mice compared to the control group.**

4. The structure activity relationships actually decrease the weight-of-the-evidence of diuron carcinogenicity rather than increase the weight.

RRB2 Response: This issue has been reviewed and addressed by the MTARC. Please see above RRB2 response #2.

5. New guidelines are in place that separate the 'known' from 'likely' category.

RRB2 Response: The 1999 Guidelines for Carcinogen Risk Assessment is a preliminary draft and should not be used as a justification for cancer reclassification. The document has a notice in the front page stated that "THIS DOCUMENT IS A PRELIMINARY DRAFT. It has not been formally released by the U.S. Environmental protection Agency and should not at this stage be construed to represent Agency policy."

Additional information

6. Mouse bone marrow micronucleus assays (MRIDs 45494502-05).

RRB2 Response: Preliminary reviews have been conducted on these *in vivo* cytogenetic mutagenicity studies. No evidence of cytogenetic effect is seen in mice administered either technical grade or formulated diuron. However, these studies provide little additional information since the CARC has already concluded that there is little or no concern on mutagenic activity of diuron.

III. Conclusion

The RRB2 evaluated the submitted data with MTARC report and concluded, after consulting with the Chair of the HED CARC, that there is insufficient information to support a reclassification of cancer category for diuron at this time. Therefore, the cancer classification for diuron remains the same as "known/likely human carcinogen with a Q_1^* of 1.91×10^{-2} $(mg/kg/day)^{-1}$ be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the rat.

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